IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Tetsuya IKEMOTO et al.
Serial No. 10/086,076 Group Art Unit 1621
Filed February 28, 2002 Examiner Michael L. Shippen
For : PRODUCTION METHOD OF CITALOPRAM, INTERMEDIATE THEREFOR AND PRODUCTION METHOD OF THE INTERMEDIATE

TRANSLATOR'S DECLARATION

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of the certified copy of Japanese Patent Application No. 039936/2000 filed on February 17, 2000; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 21st day of May, 2003.

Ritsuko Arimura

Ritsuko Arimura

(Translation)

P A T E N T O F F I C E

J A P A N E S E G O V E R N M E N T

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : February 17, 2000

Application Number : 039936/2000

Applicant(s) : Sumika Fine Chemicals Co., Ltd.

September 1, 2000

Commissioner, Patent Office
Kozo OIKAWA
Certificate No. 2000-3069939

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【Deposit Ledger Number】 006965
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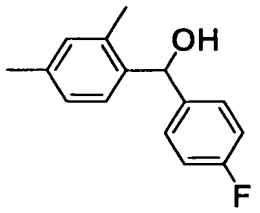
【Document】 Specification One copy
【Document】 Abstract One copy
【Number of General Power of Attorney】 9908856
【Proof】 Requested

【Document】 Specification

【Title of the Invention】 Production Method Of 5-Phthalancarbonitrile Compound, Intermediate Therefor And Production Method Thereof

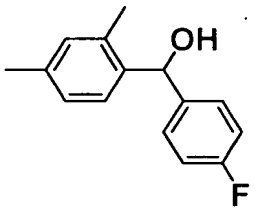
【What is Claimed is】

【Claim 1】 A compound of the formula I



I

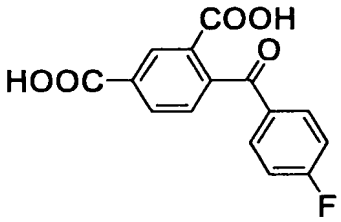
【Claim 2】 A production method of a compound of the formula I



I

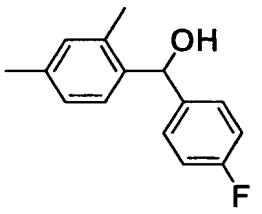
, which comprises converting 4-bromofluorobenzene to 4-fluorophenylmagnesium bromide, and reacting the 4-fluorophenylmagnesium bromide with 2,4-dimethylbenzaldehyde.

【Claim 3】 A production method of a compound of the formula II



II

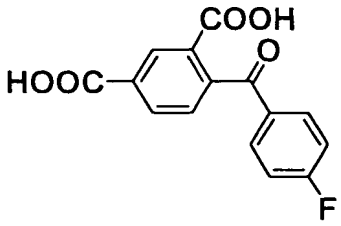
, which comprises oxidizing a compound of the formula I



I

【Claim 4】 A production method of 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene, which comprises subjecting m-xylene as a starting material and solvent to Friedel-Crafts reaction with 4-fluorobenzoyl halide.

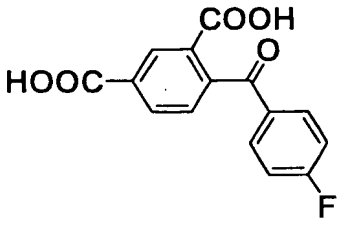
【Claim 5】 A production method of a compound of the formula II



II

, which comprises subjecting m-xylene as a starting material and solvent to Friedel-Crafts reaction with 4-fluorobenzoyl halide to give 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene and oxidizing said 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene.

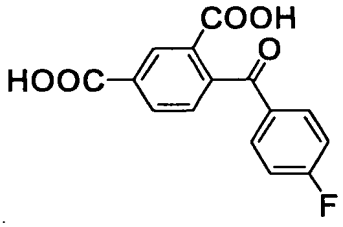
【Claim 6】 A production method of a compound of the formula II



II

, which comprises subjecting 2,4-dimethylbenzoyl halide to Friedel-Crafts reaction with fluorobenzene to give 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene and oxidizing said 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene.

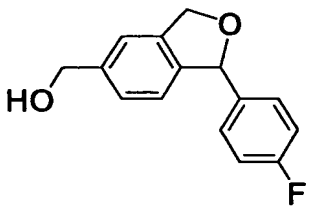
【Claim 7】 A production method of a compound of the formula II



II

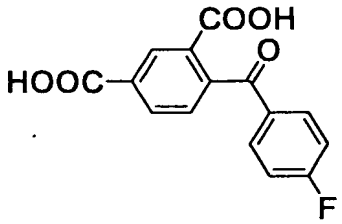
, which comprises subjecting trimellitic anhydride to Friedel-Crafts reaction with fluorobenzene in a dichloro-substituted or trichloro-substituted benzene solvent.

【Claim 8】 A production method of a compound of the formula III



III

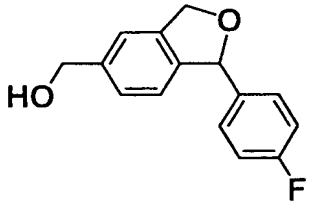
, which comprises subjecting a compound of the formula II



II

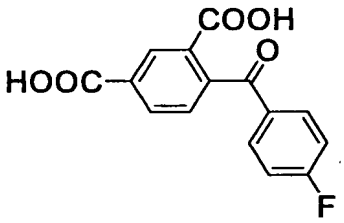
to reduction and cyclization.

【Claim 9】 A production method of a compound of the formula III



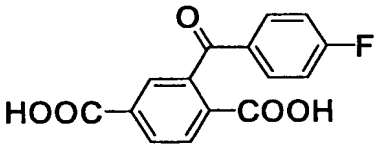
III

, which comprises subjecting trimellitic anhydride to Friedel-Crafts reaction with fluorobenzene to give a mixture of a compound of the formula II



II

and a compound of the formula IV



IV

which is an isomer thereof, subjecting the mixture to reduction and cyclization, and isolating the resulting compound.

【Claim 10】 The production method of Claim 9, wherein the reaction is carried out in dichloro-substituted or trichloro-substituted benzene.

【Claim 11】 The production method of Claim 8 or Claim 9, wherein the reduction is carried out using sodium borohydride.

【Claim 12】 The production method of Claim 8 or Claim 9, further comprising the use of a Lewis acid or dialkyl sulfate as a reaction promoter.

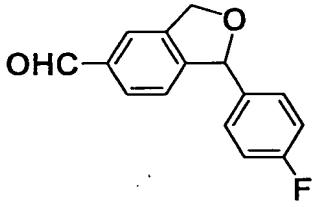
【Claim 13】 The production method of Claim 12, wherein the reaction promoter is sulfuric acid, dimethyl sulfate, diethyl sulfate or boron trifluoride.

【Claim 14】 The production method of Claim 8 or Claim 9, wherein the cyclization is carried out using an acid catalyst.

【Claim 15】 The production method of Claim 14, wherein the acid catalyst is an inorganic acid.

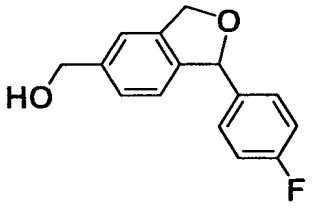
【Claim 16】 The production method of Claim 15, wherein the inorganic acid is hydrochloric acid, sulfuric acid or phosphoric acid.

【Claim 17】 A production method of a compound of the formula V



V

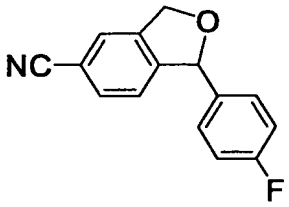
, which comprises oxidizing a compound of the formula III



III

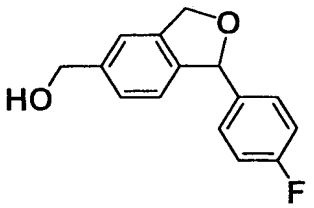
with manganese dioxide.

【Claim 18】 A production method of a 5-phthalancarbonitrile compound of the formula VI



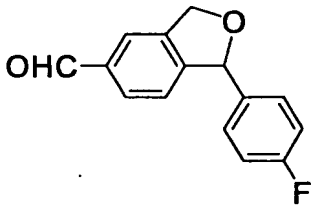
VI

, which comprises oxidizing a compound of the formula III



III

in a solvent having a boiling point of not less than 125°C at atmospheric pressure to give a compound of the formula V



V

and successively subjecting the compound to oximation reaction and dehydration reaction in the same solvent without isolation.

【Claim 19】 The production method of Claim 18, wherein the oxidation is carried out using manganese dioxide.

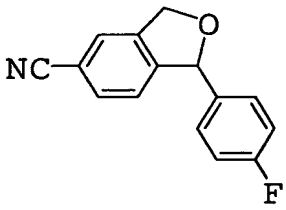
【Detailed Description of the Invention】

【Technical Field to which the Invention pertains】

The present invention relates to a production method of a 5-phthalancarbonitrile compound, which is a synthetic intermediate of citalopram useful as an antidepressant, a synthetic intermediate therefor, and a production method thereof.

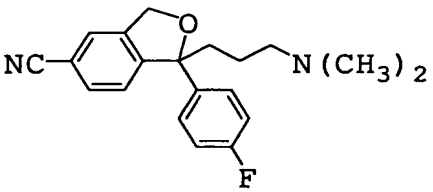
【Prior Art】

The 5-phthalancarbonitrile compound represented by the formula VI

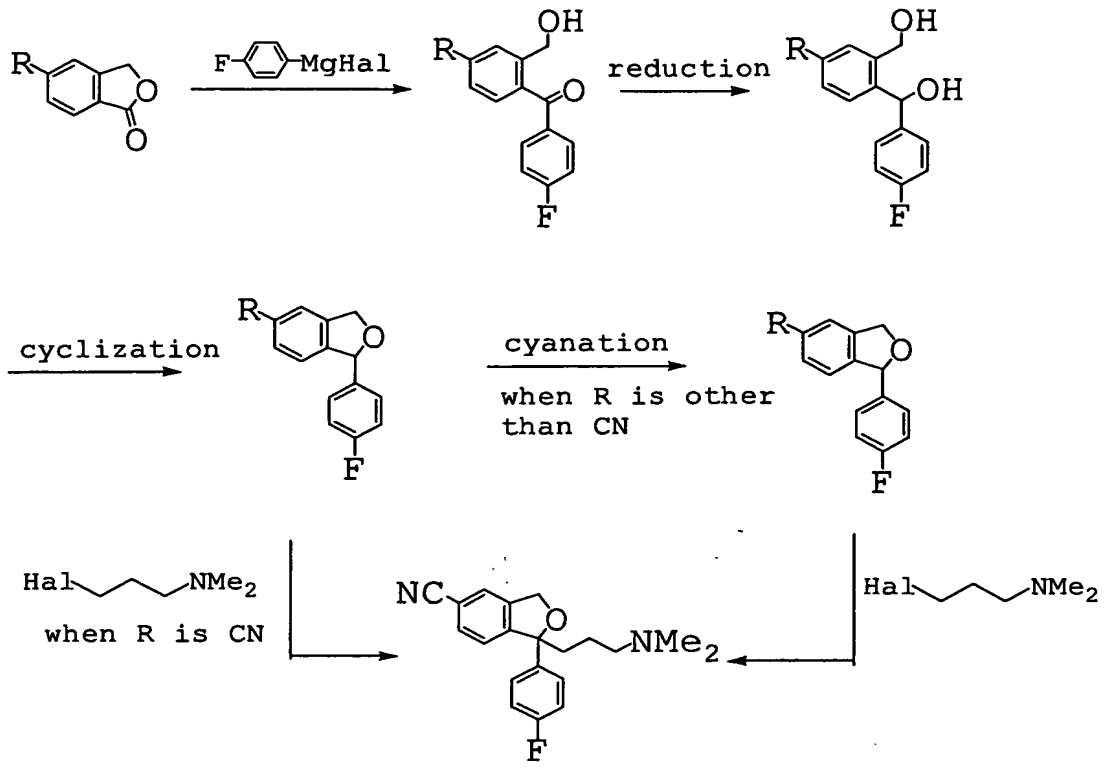


VI

is useful as a synthetic intermediate for citalopram represented by the following formula



which is useful as an antidepressant. As the production method of the 5-phthalancarbonitrile compound, the methods shown in the following scheme have been known (WO98/19511, JP-B-61-35986).



wherein R is cyano group, alkyloxycarbonyl group wherein alkyl group has 1 to 6 carbon atoms, or alkylaminocarbonyl group wherein alkyl group has 1 to 6 carbon atoms, and Hal is halogen atom.

When, in this method, R is other than cyano group, the compound needs to be reduced, ring closure, and then cyanated. When R is alkyloxycarbonyl group, cyanation is done in 3 steps of hydrolysis, amidation and reaction with chlorosulfonyl isocyanate, and when R is alkylaminocarbonyl group, cyanation is done by the reaction with thionyl chloride or phosphorus pentachloride. In these methods, environmentally unpreferable reagents such as chlorosulfonyl isocyanate, thionyl chloride and phosphorus pentachloride are used, and when R is alkyloxycarbonyl group, 3 steps are required. Accordingly, and these methods are not entirely convenient.

When R is cyano group, the production method of 5-cyanophthalide, which is a starting material, contains aspects to be improved. To be specific, 5-cyanophthalide is known to be obtained by reacting, in the presence of copper sulfate, potassium cyanide with diazonium salt derived from 5-aminophthalide (Bull. Soc. Sci. Bretagne, 26, 1951, 35). The use

of potassium cyanide and copper sulfate in this reaction makes this method an unpreferable one because toxin and heavy metal salt are used. For the synthesis of 5-aminophthalide, moreover, dangerous reaction of nitration of phthalimide (Organic Synthesis II, 459), and further, reduction to amino group with tin chloride and semi-reduction of phthalimide with zinc (J. Chem. Soc., 1931, 867) are required. From the aspect of generation of waste heavy metal, these methods are not industrially preferable.

【Problems to be Solved by the Invention】

It is an object of the present invention to provide a safe and more efficient production method of a 5-phthalancarbonitrile compound, which places only a small burden on the environmental.

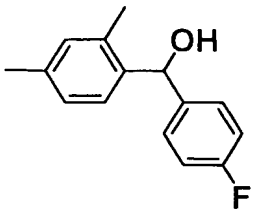
【Means of Solving the Problems】

The present inventors already reported a method based on a completely new strategy of going through a compound of the formula III to be mentioned below (also referred to as compound III), as a safe production method of 5-phthalancarbonitrile compound, which places only a small burden on the environment, in Japanese Patent Application No. 11-311703. This time, the present inventors further studied the production method of 5-phthalancarbonitrile compound using compound III as an intermediate, and found a method that performs the steps of producing a 5-phthalancarbonitrile compound from compound III more efficiently, and found that compound III, which is said intermediate, can be produced by a new method, which resulted in the completion of the present invention.

In other words, they have found a method for efficiently producing a 5-phthalancarbonitrile compound from compound III. They have found that compound III can be conveniently produced using a compound of the formula II to be mentioned below (also referred to as compound II) as a starting material, and that the compound II can be produced safely using a compound of the formula I' to be mentioned below or trimellitic anhydride as starting materials, with only a small burden on the environment. They have also found that compound II can be produced safely using a novel compound represented by the formula I as a starting material, with only a small burden on the environment.

Accordingly, the present invention relates to

(1) a compound of the formula I

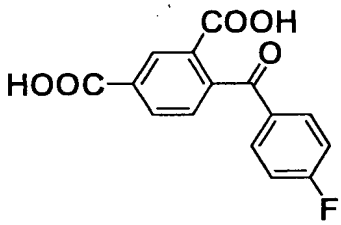


I

(hereinafter to be also referred to as compound I),

(2) a production method of a compound I, which comprises converting 4-bromofluorobenzene to 4-fluorophenylmagnesium bromide, and reacting the 4-fluorophenylmagnesium bromide with 2,4-dimethylbenzaldehyde,

(3) a production method of a compound II of the formula II



II

, which comprises oxidizing a compound I,

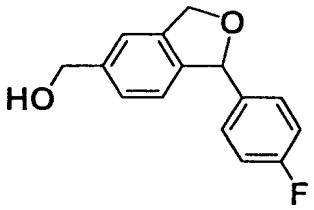
(4) a production method of 1,3-dimethyl-4-(4'-fluorobenzoyl)-benzene (hereinafter to be also referred to as compound I'), which comprises subjecting m-xylene as a starting material and solvent to Friedel-Crafts reaction with 4-fluorobenzoyl halide,

(5) a production method of a compound II, which comprises subjecting m-xylene as a starting material and solvent to Friedel-Crafts reaction with 4-fluorobenzoyl halide to give compound I' and oxidizing said compound I',

(6) a production method of a compound II, which comprises subjecting 2,4-dimethylbenzoyl halide to Friedel-Crafts reaction with fluorobenzene to give compound I' and oxidizing said compound I',

(7) a production method of a compound II, which comprises subjecting trimellitic anhydride to Friedel-Crafts reaction with fluorobenzene in a dichloro-substituted or trichloro-substituted benzene solvent,

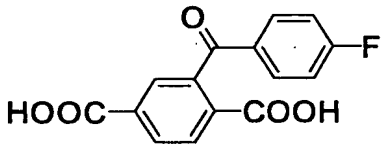
(8) a production method of a compound III of the formula III



III

, which comprises subjecting a compound II to reduction and cyclization,

(9) a production method of a compound III, which comprises subjecting trimellitic anhydride to Friedel-Crafts reaction with fluorobenzene to give a mixture of a compound II and a compound of the formula IV



IV

(hereinafter to be also referred to as compound IV), which is an isomer thereof, subjecting the mixture to reduction and cyclization, and isolating the resulting compound,

(10) the production method of (9) above, wherein the reaction is carried out in dichloro-substituted or trichloro-substituted benzene,

(11) the production method of (8) or (9) above, wherein the reduction is carried out using sodium borohydride,

(12) the production method of (8) or (9) above, further comprising the use of a Lewis acid or dialkyl sulfate as a reaction promoter,

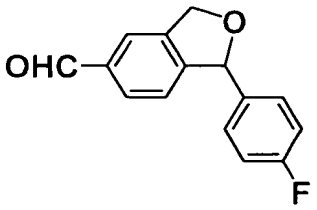
(13) the production method of (12) above, wherein the reaction promoter is sulfuric acid, dimethyl sulfate, diethyl sulfate or boron trifluoride,

(14) the production method of (8) or (9) above, wherein the cyclization is carried out using an acid catalyst,

(15) the production method of (14) above, wherein the acid catalyst is an inorganic acid,

(16) the production method of (15) above, wherein the inorganic acid is hydrochloric acid, sulfuric acid or phosphoric acid,

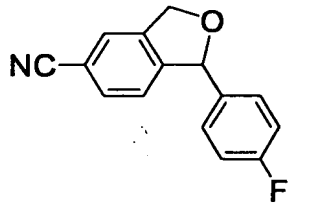
(17) a production method of a compound of the formula V



V

(hereinafter to be also referred to as compound V), which comprises oxidizing a compound III with manganese dioxide,

(18) a production method of a 5-phthalancarbonitrile compound of the formula VI



VI

(hereinafter to be also referred to as compound VI), which comprises oxidizing a compound III in a solvent having a boiling point of not less than 125°C at atmospheric pressure to give a compound V and successively subjecting the compound to oximation reaction and dehydration reaction in the same solvent without isolation, and

(19) the production method of (18) above, wherein the oxidation is carried out using manganese dioxide.

【Mode of Embodiment of the Invention】

The present invention is explained in detail in the following.

Production method of novel compound I

The compound I is novel and can be produced by, for example, a Grignard reaction of 2,4-dimethylbenzaldehyde with a Grignard reagent of 4-bromofluorobenzene. To be specific, for example, a Grignard reagent of 4-bromofluorobenzene is prepared in a reaction solvent, to which is added, preferably by dropwise addition, 2,4-dimethylbenzaldehyde to give compound I. The order of addition of the reaction reagents is subject to no particular limitation.

Production of the Grignard reagent of 4-bromofluorobenzene can follow a conventional known production method of Grignard reagent, which can be carried out easily by, for example, dispersing metal magnesium in an organic solvent and dropwise

addition of 4-bromofluorobenzene thereto generally at a temperature of from -30°C to 100°C, preferably 15°C-70°C. The amount of the metal magnesium to be used is that necessary for conversion of 4-bromofluorobenzene to a Grignard reagent, which is, for example, generally 0.9 mol-2 mol, preferably 0.95 mol-1.3 mol, per 1 mol of 4-bromofluorobenzene.

2,4-Dimethylbenzaldehyde is used in an amount of generally 0.5 mol-2 mol, preferably 0.8 mol-1.2 mol, per 1 mol of 4-bromofluorobenzene.

The reaction solvent in this reaction is subject to no particular limitation as long as it does not interfere with the Grignard reaction. A solvent which can be used for the preparation of a Grignard reagent can be applied to the Grignard reaction without isolation after preparation of the Grignard reagent, thereby preferably making the reaction step simple. Preferable solvent may be, for example, ether solvent (e.g., diethyl ether, diisopropyl ether, dibutyl ether, dipentyl ether, dihexyl ether, t-butyl methyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxolan etc.) and the like, with preference given to tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether and diethylene glycol dimethyl ether. The amount of the reaction solvent to be used in this reaction to be used is 1 L-30 L, preferably 3 L-20 L, per 1 kg of 4-bromofluorobenzene.

The temperature of this reaction is, for example, from -30°C to 100°C, preferably from -10°C to 50°C, and the reaction time is 5 min-6 hr, preferably 10 min-3 hr.

After inactivation of the Grignard reagent by the addition of water etc. to the reaction mixture, compound I can be isolated by a conventional method (e.g., extraction). After the isolation, it can be purified by a conventional method. Alternatively, it can be used in the next reaction without purification.

The compound I of the present invention may be present as an optically active compound or racemate due to an asymmetric carbon to which hydroxyl group is bonded. The racemate can be resolved into each optically active compound by a known method.

Novel production method of compound I' using m-xylene as starting material

Method 1 (m-xylene as a starting material and solvent)

As taught in USP 3835167, compound I' can be produced by Friedel-Crafts reaction of m-xylene with 4-fluorobenzoyl chloride. In this publication, dichloromethane is used as a solvent, which is unpreferable from the aspect of the influence on the environment. Thus, the present inventors have intensively investigated a solvent that can be used for this method and is environmentally preferable, and found that compound I' is produced in a high yield by the use of m-xylene as a starting material and solvent. That is, 4-fluorobenzoyl halide is subjected to Friedel-Crafts reaction using m-xylene as a starting material and solvent to give compound I' in a high yield.

To be specific, Lewis acid or Brönsted acid is dispersed in m-xylene, and 4-fluorobenzoyl halide is added, preferably by dropwise addition, thereto, or Lewis acid or Brönsted acid is added, preferably by dropwise addition, to a solution of 4-fluorobenzoyl halide in m-xylene to give compound I' in a high yield.

The halide moiety of 4-fluorobenzoyl halide in Method 1 is subject to no particular limitation, and is exemplified by fluorine atom, chlorine atom, bromine atom and iodine atom, with preference given to chlorine atom.

In Method 1, the amount of m-xylene to be used as a starting material and solvent is 3 L-30 L, preferably 5 L-15 L, per 1 kg of 4-fluorobenzoyl halide.

The Lewis acid used in Method 1 is subject to no particular limitation as long as it is generally used for Friedel-Crafts reaction, and is exemplified by aluminum chloride, aluminum bromide, zinc fluoride, zinc chloride, zinc bromide, zinc iodide, boron trifluoride, boron trichloride, silicon tetrachloride, titanium tetrachloride and the like, with particular preference given to aluminum chloride in view of the quick reaction it affords. The amount of Lewis acid to be used is 2 mol-6 mol, preferably 3 mol-4 mol, per 1 mol of 4-fluorobenzoyl halide.

The Brönsted acid used in Method 1 is subject to no particular limitation as long as it is generally used for

Friedel-Crafts reaction, and is exemplified by hydrogen fluoride, sulfuric acid, polyphosphoric acid, trifluoromethanesulfonic acid and the like, with preference given to trifluoromethanesulfonic acid. The amount of the Brönsted acid to be used is 0.0001 mol-1 mol, preferably 0.01 mol-0.2 mol, per 1 mol of 4-fluorobenzoyl halide.

In Method 1, the reaction temperature is from -20°C to 120°C, preferably 10°C-50°C, and the reaction time is 0.5 hr-15 hr, preferably 2 hr-8 hr.

The compound I' can be isolated and purified by a conventional method. For example, the reaction mixture is poured into hydrochloric acid and the organic layer obtained by separation is washed with water or aqueous alkali solution. The solvent is evaporated to isolate compound I'. The isolated product can be further purified by a conventional method, or may be used as it is in the next reaction without purification. By this method, an isomer of compound I', 1,4-dimethyl-2-(4'-fluorobenzoyl)benzene, is concurrently obtained, but can be easily separated by a conventional method such as recrystallization. The compound I' may be subjected to the next reaction without separation of the isomer.

Method 2 (Friedel-Crafts reaction of 2,4-dimethylbenzoyl chloride with fluorobenzene)

The compound I' can be also produced by Friedel-Crafts reaction of 2,4-dimethylbenzoyl chloride with fluorobenzene in a reaction solvent. The reaction solvent may be fluorobenzene (Method 2-1) or a solvent generally used for Friedel-Crafts reaction (Method 2-2). Specifically, in the case of Method 2-1, Lewis acid or Brönsted acid is dispersed in fluorobenzene and 2,4-dimethylbenzoyl chloride is added, preferably added dropwise, thereto, or Lewis acid or Brönsted acid is added to a mixture of fluorobenzene and 2,4-dimethylbenzoyl chloride, and in the case of Method 2-2, fluorobenzene is diluted in a solvent generally used for Friedel-Crafts reaction, Lewis acid or Brönsted acid is dispersed in this solution, and 2,4-dimethylbenzoyl chloride is added, preferably added dropwise, thereto, or fluorobenzene and 2,4-dimethylbenzoyl chloride are added to a solvent generally used for Friedel-Crafts reaction for dissolution and Lewis acid

or Brönsted acid is added thereto, to give compound I' in a high yield.

The amount of fluorobenzene to be used in Method 2-1 is 2 L-20 L, preferably 4 L-10 L, per 1 kg of 2,4-dimethylbenzoyl chloride.

The amount of fluorobenzene to be used in Method 2-2 is 1 mol-5 mol, preferably 1 mol-3 mol, per 1 mol of 2,4-dimethylbenzoyl chloride.

The solvent generally used for Friedel-Crafts reaction in Method 2-2 is exemplified by methylene chloride, 1,2-dichloroethane, nitrobenzene, carbon disulfide and the like, with preference given to dichloro-substituted benzene and trichloro-substituted benzene from the aspect of the environment, with particular preference given to 1,2-dichlorobenzene. The amount of the reaction solvent to be used is 1 L-20 L, preferably 5 L-15 L, per 1 kg of 2,4-dimethylbenzoyl chloride.

The Lewis acid to be used in Method 2-1 and Method 2-2 is subject to no particular limitation as long as it is generally used for Friedel-Crafts reaction, and is exemplified by aluminum chloride, aluminum bromide, zinc fluoride, zinc chloride, zinc bromide, zinc iodide, boron trifluoride, boron trichloride, silicon tetrachloride, titanium tetrachloride and the like, with preference given to aluminum chloride in view of the quick reaction it provides. The amount of the Lewis acid to be used is 0.8 mol-3 mol, preferably 1 mol-1.5 mol, per 1 mol of 2,4-dimethylbenzoyl chloride.

The Brönsted acid used in Method 2-1 and Method 2-2 is subject to no particular limitation as long as it is generally used for Friedel-Crafts reaction, and is exemplified by hydrogen fluoride, sulfuric acid, polyphosphoric acid, trifluoromethanesulfonic acid and the like, with preference given to trifluoromethanesulfonic acid. The amount of the Brönsted acid to be used is 0.0001 mol-1 mol, preferably 0.01 mol-0.5 mol, per 1 mol of 2,4-dimethylbenzoyl chloride.

In Method 2-1 and Method 2-2, the reaction temperature is from -20°C to 100°C, preferably 0°C-90°C, and the reaction time is 0.5 hr-10 hr, preferably 1 hr-4 hr.

The compound I' can be isolated and purified by a

conventional method. For example, the reaction mixture is poured into hydrochloric acid and the organic layer obtained by separation is washed with water or aqueous alkali solution. The solvent is evaporated to isolate compound I'.

Production method of compound II

Method 1 (production method of compound II using compound I as starting material)

The compound II can be obtained by oxidation of compound I. The oxidation of compound I is performed using, for example, an oxidizing agent. To be specific, a solution of compound I and a solution or a dispersion of the oxidizing agent are mixed and stirred to give compound II. The solvent for these solution and dispersion is exemplified by the following reaction solvents.

The oxidizing agent is subject to no particular limitation as long as it allows oxidation of methyl group and hydroxyl group into carboxyl group and acyl group, respectively. Examples of the oxidizing agent include permanganate, dichromate and the like. Considering the influence on the environment and toxicity, permanganate (e.g., potassium permanganate and the like) is preferable. While permanganate used for oxidation reaction causes side production of manganese dioxide, manganese dioxide can be used again as an oxidizing agent for synthesis of compound V from compound III to be mentioned later. Therefore, permanganate is preferably used because manganese dioxide does not need to be wasted and the production cost can be reduced. The amount of the oxidizing agent to be used in Method 1 is 3 mol-15 mol, preferably 4.6 mol-10 mol, per 1 mol of compound I.

In Method 1, the reaction solvent is subject to no particular limitation as long as it is hardly oxidized by the oxidizing agent to be used for the oxidation reaction. Examples thereof include water, t-butyl alcohol, t-amyl alcohol, acetone, ethyl methyl ketone, isobutyl methyl ketone, methylene chloride, chloroform, 1,2-dichloroethane, benzene, monochlorobenzene, 1,2-dichlorobenzene, acetic acid, propionic acid, butyric acid and the like, and mixed solvents thereof, with preference given to water, t-butyl alcohol, a mixed solvent of water and t-butyl alcohol, t-amyl alcohol, a mixed solvent of water and t-amyl alcohol, acetone and a mixed solvent of water and acetone. The

amount of the solvent to be used is 5 L-50 L, preferably 8 L-24 L, per 1 kg of compound I.

In Method 1, the reaction temperature is 0°C-120°C, preferably 50-100°C, and the reaction time is 0.5 hr-12 hr, preferably 2 hr-8 hr.

The compound II can be isolated by a conventional method. For example, the reaction mixture is filtrated to remove insoluble matter (inclusive of manganese dioxide), a typical inorganic acid (e.g., hydrochloric acid, sulfuric acid etc.) is added to the filtrate and the precipitated compound II is collected by filtration. After the isolation, it is further purified by a conventional method. Alternatively, it can be used in the next reaction without purification.

Method 2 (production method of compound II using compound I' as starting material)

The compound II can be also obtained by oxidation of compound I', wherein the oxidation can be performed by the use of an oxidizing agent. In Method 2, the amount of the oxidizing agent to be used is 2.5 mol-14 mol, preferably 4 mol-9 mol, per 1 mol of compound I', and the amount of the solvent to be used is 5 L-50 L, preferably 8 L-24 L, per 1 kg of compound I'. Other factors such as reaction conditions, isolation conditions and the like are the same as those employed for the oxidation reaction in the above-mentioned Method 1. The isolated product can be purified by a conventional method. Alternatively, it can be used in the next reaction without purification.

Method 3 (production method of compound II using trimellitic anhydride as starting material)

USP 3835167 teaches Friedel-Crafts reaction of trimellitic anhydride and benzene. According to the method disclosed in this publication, nitrobenzene is used as a solvent, which is unpreferable from the aspect of the environment. According to the present invention, the reaction in this publication is carried out using fluorobenzene instead of benzene and under the same conditions or at a higher temperature, whereby the progress of the Friedel-Crafts reaction is mostly prevented (see Comparative Example 1). The present inventors have studied a solvent that allows smooth progress of the Friedel-Crafts reaction of

trimellitic anhydride and fluorobenzene, and that is environmentally preferable, and found dichloro-substituted benzene and trichloro-substituted benzene to be most suitable. That is, trimellitic anhydride and fluorobenzene are subjected to Friedel-Crafts reaction in a dichloro-substituted or trichloro-substituted benzene solvent to give compound II environmentally preferably and smoothly.

To be specific, for example, trimellitic anhydride and fluorobenzene are dispersed in a reaction solvent, Lewis acid or Brönsted acid is added thereto and the mixture is stirred to give compound II.

In Method 3, the amount of fluorobenzene to be used is 1 mol-10 mol, preferably 1.2 mol-3 mol, per 1 mol of trimellitic anhydride.

The reaction solvent in Method 3, dichloro-substituted or trichloro-substituted benzene, may be, for example, 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,2,4-trichlorobenzene, 1,2,3-trichlorobenzene and the like, with particular preference given to 1,2-dichlorobenzene because it produces compound II relatively highly selectively. The amount of the reaction solvent to be used is 5 L-40 L, preferably 10 L-25 L, per 1 kg of trimellitic anhydride. Other than the above-mentioned solvents, certain solvents can accelerate the reaction in Method 3. Examples thereof include methylene chloride, 1,2-dichloroethane, nitrobenzene, carbon disulfide and the like, with preference given to methylene chloride and 1,2-dichloroethane. The amount of the solvent to be used is 4 L-40 L, preferably 8 L-25 L, per 1 kg of trimellitic anhydride.

In Method 3, the Lewis acid is subject to no particular limitation as long as it is generally used for Friedel-Crafts reaction. Examples thereof include aluminum chloride, aluminum bromide, zinc fluoride, zinc chloride, zinc bromide, zinc iodide, boron trifluoride, boron trichloride, silicon tetrachloride, titanium tetrachloride and the like, with particular preference given to aluminum chloride in view of the quick reaction it provides. The amount of the Lewis acid to be used is 2.5 mol-5 mol, preferably 3 mol-3.5 mol, per 1 mol of trimellitic anhydride.

The Brönsted acid used in the Method is subject to no

particular limitation as long as it is generally used for Friedel-Crafts reaction, and is exemplified by hydrogen fluoride, sulfuric acid, polyphosphoric acid, trifluoromethanesulfonic acid and the like, with preference given to trifluoromethanesulfonic acid. The amount of the Brönsted acid to be used is 0.0001 mol-1 mol, preferably 0.01 mol-0.2 mol, per 1 mol of trimellitic anhydride.

In Method 3, the reaction temperature is 40°C-150°C, preferably 70°C-120°C, and the reaction time is 0.5 hr-16 hr, preferably 2 hr-9 hr.

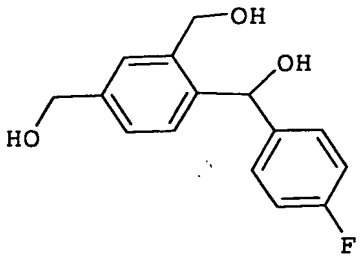
In the Method, compound II is obtained as a mixture with its isomer, compound IV. This mixture can be easily separated from the reaction mixture according to a conventional method. For example, the reaction mixture is poured into an acidic aqueous solution such as aqueous hydrochloric acid solution, aqueous sulfuric acid solution and the like and partitioned to separate an organic layer, which is, after extraction with an aqueous alkali solution, neutralized with an acidic aqueous solution to separate the mixture. The compound II and compound IV can be separated by recrystallization and the like. The compound II can be used as a mixture in the next reaction. The mixture can be used in the next reaction without purification.

Novel production method of compound III

The compound III has been disclosed in JP Application No. 11-311703 by the present inventors, Ikemoto and Igi, as an important intermediate for efficient synthesis of compound VI which is a citalopram precursor. The present inventors have studied a method for producing compound III by a new route and found compound II to be a precursor of compound III, as well as a simple and easy production method of compound III from compound II. That is, compound III can be easily obtained by reduction and cyclization of compound II. The order of the reduction and cyclization is subject to no particular limitation. Cyclization after reduction of compound II, or cyclization after partial reduction (reduction of ketone) of compound II, followed by reduction may be employed. Cyclization after reduction is preferable because it requires a short reaction step. The starting material compound II can be used as a mixture with an

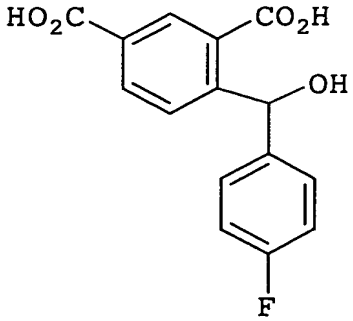
isomer, compound IV, for the production of compound III. When the mixture is subjected to reduction and cyclization, compound III is isolated after reduction and cyclization. When compared with the yield of compound III when it is obtained by isolation followed by reduction and cyclization, the yield is higher by the former route.

The compound obtained by reduction of compound II is represented by the formula VII



VII

(hereinafter to be also referred to as compound VII). When cyclization is conducted after partial reduction of compound II, and further reduction is applied, various intermediates are present, such as a compound of the formula



and the like. The production of compound III from compound II in the present invention consists of two steps of (1) reduction and (2) cyclization.

When cyclization follows reduction, the reaction conditions of (1) may lead to the simultaneous production of compound VII and compound III, in which case (2) can be omitted depending on the proportion of compound III produced.

The following explains a method for producing compound III by cyclization after reduction of compound II.

The conditions of (1) are as follows.

The compound II can be reduced in the same manner as in the generally known reduction of carboxylic acid into alcohol, for example, by the use of a reducing agent. To be specific, a

reducing agent is dispersed in a reaction solvent, and compound II is added, preferably by dropwise addition, to the dispersion to give compound VII. This reduction is preferably conducted using a suitable catalyst in addition to the reducing agent. The catalyst is preferably added after the addition of a reducing agent and compound II.

The reducing agent in (1) is subject to no particular limitation as long as it is generally used for the conversion of carboxylic acid to alcohol. Examples thereof include sodium borohydride, lithium aluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, borane-THF complex, borane-dimethyl sulfide complex and the like, with particular preference given to sodium borohydride. The amount of the reducing agent to be used is 1.25 mol-7.5 mol, preferably 2.5 mol-5 mol, per 1 mol of compound II.

The catalyst in (1) is exemplified by inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, boric acid, nitric acid etc.), organic acid (e.g., acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, benzoic acid etc.), Lewis acid (e.g., boron trifluoride, boron trichloride, boron tribromide, zinc fluoride, zinc chloride, zinc bromide, zinc iodide, aluminum fluoride, aluminum chloride, aluminum bromide, magnesium fluoride, magnesium chloride, magnesium bromide, magnesium iodide, silicon tetrachloride, titanium tetrachloride etc.), dialkyl sulfate (e.g., dimethyl sulfate, diethyl sulfate etc.) and the like, with preference given to Lewis acid and dialkyl sulfate in view of an increased yield and selectivity, with more preference given to sulfuric acid, boron trifluoride, dimethyl sulfate and diethyl sulfate for higher yield. The amount of the catalyst to be used is 1.25 mol-7 mol, preferably 2 mol-6 mol, per 1 mol of compound II.

The reaction solvent in (1) is subject to no particular limitation as long as it hardly shows reaction under the conditions of reduction. Preferred are ether solvents. Examples of the ether solvent include diethyl ether, diisopropyl ether, dibutyl ether, dipentyl ether, dihexyl ether, t-butyl methyl

ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxolan and the like, with more preference given to tetrahedrofuran, diethyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, t-butyl methyl ether, dibutyl ether and the like, and with particular preference given to tetrahydrofuran, t-butyl methyl ether, dibutyl ether, ethylene glycol dimethyl ether and diethylene glycol dimethyl ether. The amount of the reaction solvent to be used is 1 L-40 L, preferably 5 L-20 L, per 1 kg of compound II.

In (1), the reaction temperature is from -20°C to 120°C, preferably 25°C-75°C, and the reaction time is 0.5 hr-10 hr, preferably 2 hr-7 hr.

The compound VII can be isolated and purified by a conventional method. For example, water is added to the obtained reaction mixture, and the mixture is cooled to allow crystal precipitation. The reaction mixture containing compound VII can be used in the next reaction as it is without isolation of compound VII. Alternatively, a reaction mixture wherein the reducing agent has been inactivated with water can be used in the next reaction.

The following explains (2).

Cyclization of compound VII is conducted via dehydration reaction by applying a heat. In this case, for acceleration of the reaction, further addition of an acid catalyst is preferable. To be specific, for example, an acid catalyst is added to the reaction mixture obtained in (1) or a mixture of the reaction solvent and compound VII, to give compound III.

The acid catalyst in (2) is exemplified by inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, boric acid, nitric acid etc.), organic acid (e.g., acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, benzoic acid etc.), Lewis acid (e.g., boron trifluoride, boron trichloride, boron tribromide, zinc fluoride, zinc chloride, zinc bromide, zinc iodide, aluminum fluoride, aluminum chloride, aluminum bromide, magnesium fluoride,

magnesium chloride, magnesium bromide, magnesium iodide, silicon tetrachloride, titanium tetrachloride and the like), with more preference given to inorganic acid, particularly preferably hydrochloric acid, sulfuric acid and phosphoric acid. The amount of the acid catalyst to be used is 0.01 kg-50 kg, preferably 0.5 kg-5 kg, per 1 kg of compound II which is a starting material in (1).

The cyclization reaction tends to proceed by the presence of the above-mentioned acid catalyst. The use of the above-mentioned acid catalyst as a catalyst in (1) often advances not only the reduction reaction but also cyclization reaction. Thus, the use of an excess acid catalyst as a catalyst in the reduction reaction of (1) enables synthesis of compound III in one pot. In this case, the amount of catalyst to be used in (1) is 2 mol-30 mol, preferably 3 mol-15 mol, per 1 mol of compound II which is a starting material in (1).

The solvent in (2) is subject to no particular limitation as long as it does not interfere with the reaction. Preferred are the solvents used in (1), and a mixed solvent of the solvent used in (1) and water. The use of such solvents is preferable because the obtained reaction mixture can be applied to the step of (2) after the completion of the reaction of (1) without isolation of compound VII from the reaction mixture, and the reaction mixture containing water to inactivate the reducing agent after the completion of the reaction of (1) can be applied as it is to the step of (2), which means that the isolation and purification of compound VII can be omitted. When water is added, only the solvent used for the reaction mixture of (1) can be evaporated to leave only water, and said water or a mixture of said water and a suitable solvent other than the solvent used in (1) can be used as the solvent in (2). Examples of the suitable solvent other than the solvent used in (1) is subject to no particular limitation. Examples thereof include hydrocarbon solvents (e.g., toluene, xylene, mesitylene, hexane, heptane, octane etc.) and the like. The amount thereof is 0.5 L-20 L, preferably 3 L-10 L, per 1 kg of compound II which is a starting material in (1).

In (2), the reaction time is generally 0.5 hr-15 hr, preferably 1 hr-7 hr, and the reaction temperature is generally

10°C-100°C, preferably 20°C-70°C.

The compound III can be isolated by a conventional method, for example, by adding water to the reaction mixture, cooling the mixture and collecting the resulting crystals by filtration. After the isolation, compound III can be further purified by a conventional method. Alternatively, it can be used in the next reaction without purification.

A method comprising cyclization after partial reduction of compound II and further reduction, is performed in the same manner as in the above-mentioned method by the selection of reaction reagents (e.g., reducing agent) generally used for desired partial reduction and cyclization.

Novel production method of compound V

The compound V is useful as an intermediate for the efficient synthesis of compound VI which is a precursor of citalopram. The method for efficient synthesis of compound V is important because it eventually contributes greatly to the efficient synthesis of citalopram. It is known that compound V can be obtained by oxidation of compound III using an oxidizing agent (JP application No. 11-311703). The positions of compound III that are easily oxidized are 5-position hydroxymethyl group of 1,3-dihydroisobenzofuran ring, and the 1-position and 3-position carbons. Therefore, it is worried that the oxidation of compound III may result in the oxidation of the 1-position and 3-position carbons besides the 5-position hydroxymethyl group. The present inventors have intensively studied with the aim of resolving such concern and found that the use of manganese dioxide as an oxidizing agent results in the production of compound V in a high yield almost without any side reaction (oxidation of the 1-position and 3-position carbons). That is, by the use of manganese dioxide as an oxidizing agent for the oxidation of compound III, compound V can be obtained in a high yield. To be specific, compound III is dissolved or dispersed in a suitable solvent and manganese dioxide is added thereto to give compound V. The order of addition and the like are subject to no particular limitation.

The amount of the manganese dioxide to be used for this reaction is 1 kg-20 kg, preferably 3 kg-10 kg, per 1 kg of

compound III.

The solvent to be used for this reaction is subject to no particular limitation as long as it is not easily subject to oxidation, and is exemplified by ethers (e.g., diethyl ether, diisopropyl ether, dibutyl ether, dipentyl ether, dihexyl ether, t-butyl methyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxolan etc.), ketones (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-pentanone, 3-pentanone, cyclopentanone, cyclohexanone etc.), esters (e.g., ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, amyl acetate, isoamyl acetate, benzyl acetate, phenyl acetate, methyl propionate, ethyl propionate, propyl propionate, isopropyl propionate, butyl propionate, isobutyl propionate, amyl propionate, isoamyl propionate, benzyl propionate, phenyl propionate, methyl butyrate, ethyl butyrate, propyl butyrate, isopropyl butyrate, butyl butyrate, isobutyl butyrate, amyl butyrate, isoamyl butyrate, benzyl butyrate, phenyl butyrate etc.), lactones (e.g., γ-butyrolactone etc.), carbonates (e.g., dimethyl carbonate, diethyl carbonate, ethylene carbonate etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, mesitylene, ethylbenzene, t-butylbenzene etc.), aliphatic hydrocarbons (e.g., pentane, hexane, isohexane, heptane, isoheptane, octane, isooctane, nonane, decane, undecane, dodecane, petroleum ether etc.), halogen substituted aromatic hydrocarbons (e.g., monochlorobenzene, 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,2,4-trichlorobenzene, 1,2,3-trichlorobenzene etc.), halogen substituted aliphatic hydrocarbons (e.g., dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,1-trichloroethane, 1-chloropropane, 2-chloropropane etc.), amide solvents (e.g., dimethylformamide, dimethylacetamide, N-methylpyrrolidone etc.), sulfur-containing solvents (e.g., dimethyl sulfoxide, sulforane etc.), and the like. Of these, particularly preferable solvents are t-butyl methyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, toluene, xylene, mesitylene, dichloromethane and monochlorobenzene. The amount of the solvent to be used is 3 L-50

L, preferably 5 L-20 L, per 1 kg of compound III.

In this reaction, the reaction temperature is from -10°C to 100°C, preferably 10°C-60°C, and the reaction time is 1 hr-24 hr, preferably 2 hr-8 hr.

The compound V can be isolated by a conventional method comprising, for example, filtration of the reaction mixture, and evaporation of the solvent from the obtained filtrate. After filtration of the reaction mixture, it can be used in the next reaction without evaporation of the solvent from the resulting filtrate. The waste manganese compound thus filtered off can be reprocessed and recycled for use as permanganate or manganese dioxide by a conventional method, which is environmentally preferable.

Novel production method of compound VI

The compound VI is a useful intermediate as a precursor of citalopram. It is known that the compound VI can be obtained by successive oxidation, oximation and dehydration of compound III as a starting compound. The present inventors have intensively studied a production method that produces compound VI easily and efficiently and found that a solvent having a boiling point of not less than 125°C at the atmospheric pressure can be used as the solvent throughout the above-mentioned production route. That is, compound III is oxidated in the solvent to give a solution of compound V in the solvent, without isolating compound V, oximated and dehydrated successively in the same solvent. Thereby, compound VI is produced easily and efficiently. To be specific, compound III and an oxidizing agent are added to a solvent having a boiling point of not less than 125°C at the atmospheric pressure to allow oxidation reaction. After the completion of the oxidation reaction, the oxidizing agent is filtered off and hydroxylamine or a hydrochloride thereof is added to the resulting filtrate to allow oximation reaction. Finally, a dehydrating agent is added to the obtained reaction mixture for a dehydration reaction to give compound VI. According to the method of the present invention, oxidation, oximation and dehydration reaction can be conducted in a single solvent.

The solvent having a boiling point of not less than 125°C at the atmospheric pressure is subject to no particular

limitation and is exemplified by ethers (e.g., dibutyl ether, dipentyl ether, dihexyl ether, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether etc.), ketones (e.g., cyclopentanone, cyclohexanone etc.), esters (e.g., amyl acetate, isoamyl acetate, benzyl acetate, phenyl acetate, butyl propionate, isobutyl propionate, amyl propionate, isoamyl propionate, benzyl propionate, phenyl propionate, butyl butyrate, isobutyl butyrate, amyl butyrate, isoamyl butyrate, benzyl butyrate, phenyl butyrate etc.), lactones (e.g., γ-butyrolactone etc.), carbonates (e.g., diethyl, carbonate, ethylene carbonate etc.), aromatic hydrocarbons (e.g., xylene, mesitylene, ethylbenzene, t-butylbenzene etc.), halogen substituted aromatic hydrocarbons (e.g., monochlorobenzene, 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,2,4-trichlorobenzene, 1,2,3-trichlorobenzene etc.), amide solvents (e.g., dimethylformamide, dimethylacetamide, N-methylpyrrolidone etc.), sulfur-containing solvents (e.g., dimethyl sulfoxide, sulforane etc.), and the like. Of these, particularly preferable solvents are diethylene glycol dimethyl ether, xylene, mesitylene, t-butylbenzene and monochlorobenzene. The amount of the solvent to be used for oxidation, oximation and dehydration reaction is 3 L-50 L, preferably 5 L-20 L, per 1 kg of compound III, the starting material.

The following explains the oxidation reaction of compound III.

The compound III can be oxidized in completely the same manner as in the above-mentioned "Novel production method of compound V" except the solvent is those mentioned above. The compound V obtained by oxidation of compound III can be used in the next oximation reaction without isolation from the reaction mixture. Note that the oxidizing agent should be removed from the reaction mixture according to a conventional method.

The following explains the oximation reaction.

The compound V can be converted to an oxime by, for example, oximation reaction with hydroxylamine or a hydrochloride thereof. To be specific, for example, the oxidizing agent is filtered off from the reaction mixture after oxidation, and hydroxylamine or a hydrochloride thereof is added to give the oxime.

The amount of hydroxylamine or a hydrochloride thereof to be used for oximation is 1 mol-5 mol, preferably 1 mol-2 mol, per 1 mol of compound III used in the oxidation step.

When a hydroxylamine hydrochloride is used, a suitable base is preferably added in 1 mol-5 mol per 1 mol of hydroxylamine hydrochloride. The base can be added, preferably dropwise, together with hydroxylamine hydrochloride or after the addition thereof. The base is subject to no particular limitation as long as it shows less influence on cyano group. Examples thereof include organic base (e.g., triethylamine, tributylamine, dimethylaniline, pyridine, sodium methoxide, sodium ethoxide, sodium t-butoxide, potassium t-butoxide etc.), inorganic base (e.g., sodium carbonate, sodium hydrogencarbonate, sodium hydroxide, potassium carbonate, potassium hydrogencarbonate, potassium hydroxide etc.) and the like, with preference given to triethylamine.

The reaction temperature of the oximation reaction is 20°C-120°C, preferably 40°C-100°C, and the reaction time is 10 min-4 hr, preferably 30 min-2 hr.

The oxime obtained from compound III can be subjected to dehydration reaction without isolation from the reaction mixture.

The following explains dehydration reaction.

The oxime obtained in the previous step can be dehydrated, for example, by the use of a dehydration agent. Specifically, for example, a dehydration agent is added to the reaction mixture after the oximation reaction to give compound VI.

Examples of the dehydration agent to be used for this dehydration step include acid anhydride (e.g., acetic anhydride, phthalic anhydride etc.), phosphorus oxychloride, methanesulfonyl chloride, p-toluenesulfonyl chloride and the like, with particular preference given to acetic anhydride in view of the environment and yield. The amount of the dehydration agent to be used is 1 mol-10 mol, preferably 2 mol-5 mol, per 1 mol of oxime.

In the dehydration reaction, the reaction temperature is 60°C-160°C, preferably 120°C-150°C, more preferably 125°C-150°C, and the reaction time is 0.5 hr-8 hr, preferably 1.5 hr-6 hr.

The compound VI can be isolated by subjecting the reaction mixture to a conventional method (e.g., neutralization,

extraction, crystallization and the like). As described above, the use of a solvent having a boiling point of not less than 125°C at the atmospheric pressure, as a solvent for oxidatron, oximation, dehydratron reaction, eliminates the need for a step for evaporating the solvent after completion of each step, whereby compound VI can be obtained easily from compound III.

From the foregoing, the method of the present invention affords safe and convenient production of compound VI, which is a precursor of citalopram, without using a reagent placing a large burden on the environment, such as highly toxic heavy metal, metal cyanide, thionyl chloride and the like.

The compound VI can be led to citalopram according to a method described in, for example, JP-B-61-35986, as a result of which citalopram useful as an antidepressant can be produced.

The present invention is explained in detail by referring to illustrative examples. The present invention is not limited by these examples in any way.

【Examples】

Example 1

Synthesis of (2,4-dimethylphenyl)-(4'-fluorophenyl)methanol (compound I)

Under a nitrogen atmosphere, turnings of magnesium (16.8 g) were dispersed in THF (116 ml), and iodine (0.1 g) was added. Under a nitrogen atmosphere, a solution of 4-bromofluorobenzene (116 g) in THF (201 ml) was added dropwise at 15-40°C, and the mixture was stirred at 20-40°C for 2 hr. The obtained mixture with a Grignard reagent was cooled and thereto was added dropwise a solution of 2,4-dimethylbenzaldehyde (81 g) in THF (81 ml) at 0-20°C. After the dropwise addition, the reaction mixture was stirred at 0-20°C for 2 hr. A saturated aqueous ammonium chloride solution was added to stop the reaction. The reaction mixture was partitioned and the obtained organic layer was retained. The aqueous layer was extracted with toluene and combined with the organic layer obtained earlier, and washed with saturated brine. The solvent was evaporated from the organic layer under reduced pressure to give (2,4-dimethylphenyl)-(4'-fluorophenyl)methanol (139.2 g, 100%) as a colorless oil.

^{1}H-NMR($CDCl_3$, 400 MHz) δ=2.05(1H,d,J=4Hz), 2.21(3H,s), 2.31(3H,s),

5.96(1H,d,J=4Hz), 6.98(1H,s), 7.00(2H,t,J=9Hz), 7.05(1H,d,J=8Hz), 7.29(2H,dd,J=9Hz,J=5Hz), 7.33(1H,d,J=8Hz)ppm

Example 2

Synthesis of 4-(4'-fluorobenzoyl)isophthalic acid (compound II)

To (2,4-dimethylphenyl)-(4'-fluorophenyl)methanol (121 g) were added t-butyl alcohol (723 ml) and water (1090 ml) and the mixture was heated to 50°C. Potassium permanganate (582 g) was added at 50-75°C over 6 hr. The reaction mixture was stirred at 70-85°C for 3 hr and most of t-butyl alcohol was evaporated under reduced pressure. The by-produced manganese dioxide was filtered off and the obtained filtrate was neutralized with 6N hydrochloric acid. The generated crystals were collected by filtration and dried to give nearly pure 4-(4'-fluorobenzoyl)-isophthalic acid (114.2 g, 75%) as white crystals.

^{1}H-NMR(DMSO-d_6, 400 MHz) δ=7.31(2H,t,J=9Hz), 7.55(1H,d,J=8Hz), 7.70(2H,dd,J=9Hz,J=5Hz), 8.23(1H,dd,J=8Hz,J=2Hz), 8.51(1H,d,J=2Hz), 13.52(2H,br)ppm

Example 3

Synthesis of 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene (compound I')

To a suspension of anhydrous aluminum chloride (19.5 g) dispersed in m-xylene (150 ml) was added dropwise 4-fluorobenzoyl chloride (21.1 g) under ice-cooling. The mixture was stirred at 0-10°C for 3 hr and poured into 6N hydrochloric acid. The reaction mixture was partitioned and the obtained organic layer was washed successively with water, 10% aqueous sodium hydroxide solution and water. The solvent was evaporated to give a 96:4 mixture (30.2g, 99%) of 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene and 1,3-dimethyl-2-(4'-fluorobenzoyl)benzene as pale-yellow oil.

1,3-Dimethyl-4-(4'-fluorobenzoyl)benzene

^{1}H-NMR($CDCl_3$, 400 MHz) δ=2.32(3H,s), 2.38(3H,s), 7.05(1H,d,J=8Hz), 7.11(2H,dd,J=9Hz,J=7Hz), 7.11(1H,s), 7.21(1H,d,J=8Hz), 7.82(2H,dd,J=9Hz,J=5Hz)ppm

Example 4

Synthesis of 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene (compound I')

To a suspension of anhydrous aluminum chloride (16.2 g) dispersed in 1,2-dichlorobenzene (150 ml) was added fluorobenzene

(13 g), and thereto was added dropwise 2,4-dimethylbenzoyl chloride (17.0 g) at 0-20°C. The mixture was stirred at 10-30°C for 1 hr and heated to 80°C. The mixture was stirred for 1 hr, cooled again and poured into 6N hydrochloric acid. The reaction mixture was diluted with a great excess toluene and partitioned. The obtained organic layer was washed successively with 5% aqueous sodium hydroxide solution and water, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane-ethyl acetate as eluent to give nearly pure 1,3-dimethyl-4-(4'-fluorobenzoyl)-benzene (19.4 g, 85%) as pale-yellow oil. The spectrum data of this oil were the same as those confirmed in Example 3.

Example 5

Synthesis of 4-(4'-fluorobenzoyl)isophthalic acid (compound II)

Potassium permanganate (45 g) was dispersed in 25 wt% aqueous t-butyl alcohol solution (110 g) and the mixture was heated to 65°C. Thereto was added dropwise a t-butyl alcohol (28 ml) solution of a 96:4 mixture, synthesized in Example 3, (10 g) of 1,3-dimethyl-4-(4'-fluorobenzoyl)benzene and 1,3-dimethyl-2-(4'-fluorobenzoyl)benzene. After the dropwise addition, the mixture was reacted at 80-85°C for 3 hr and most of t-butyl alcohol was evaporated under reduced pressure. The by-produced manganese dioxide was filtered off. The obtained filtrate was neutralized with 6N hydrochloric acid and the generated crystals were collected by filtration and dried to give nearly pure 4-(4'-fluorobenzoyl)isophthalic acid (9.9 g, 78%) as white crystals. The spectrum data of the crystals were the same as those in Example 2.

Example 6

Synthesis of 4-(4'-fluorobenzoyl)isophthalic acid (compound II)

Trimellitic anhydride (20 g) and fluorobenzene (18.5 g) were dispersed in 1,2-dichlorobenzene (200 ml) and thereto was added anhydrous aluminum chloride (42 g). The mixture was stirred at 70-90°C for 4 hr. The reaction mixture was poured into 4N hydrochloric acid (400 ml) and extracted with methyl isobutyl ketone (400 ml). The organic layer was extracted with 5% aqueous sodium hydroxide solution (240 g) and the aqueous layer was neutralized with 6N hydrochloric acid (64 g). The resulting

crystals were collected by filtration, washed with water and dried to give a 7:3 mixture (22.4 g, 75%) of 4-(4'-fluorobenzoyl)isophthalic acid and 2-(4'-fluorobenzoyl)terephthalic acid as white crystals.

The obtained mixture was recrystallized from methanol-water (8:5) to give nearly pure 4-(4'-fluorobenzoyl)isophthalic acid (6.8 g). The spectrum data of the crystals were the same as those in Example 2.

Example 7

Synthesis of 4-(4'-fluorobenzoyl)isophthalic acid (compound II)

Trimellitic anhydride (20 g) and fluorobenzene (20 g) were dispersed in 1,2,4-trichlorobenzene (150 ml) and anhydrous aluminum chloride (42 g) was added. The mixture was stirred at 70-90°C for 8 hr. The reaction mixture was poured into 4N hydrochloric acid (300 ml) in an ice bath, and the mixture was stirred at 50°C for 3 hr and cooled. The resulting crystals were thoroughly washed with water, collected by filtration and dried to give a 65:35 mixture (19.1 g, 64%) of 4-(4'-fluorobenzoyl)-isophthalic acid and 2-(4'-fluorobenzoyl)terephthalic acid as white crystals.

4-(4'-Fluorobenzoyl)isophthalic acid

^{1}H-NMR(DMSO-d_6, 400 MHz) δ=7.31(2H,t,J=9Hz), 7.55(1H,d,J=8Hz), 7.70(2H,dd,J=9Hz,J=5Hz), 8.23(1H,dd,J=8Hz,J=2Hz), 8.51(1H,d,J=2Hz), 13.52(2H,br)ppm

2-(4'-Fluorobenzoyl)terephthalic acid

^{1}H-NMR(DMSO-d_6, 400 MHz) δ=7.32(2H,t,J=9Hz), 7.71(2H,dd,J=9Hz,J=5Hz), 7.87(1H,d,J=2Hz), 8.09(1H,d,J=8Hz), 8.17(1H,dd,J=8Hz,J=2Hz), 13.52(2H,br)ppm

Example 8

Synthesis of 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (compound III)

To a suspension of sodium borohydride (2.5 g) dispersed in diethylene glycol dimethyl ether (40 ml) was added dropwise a solution of a 7:3 mixture, obtained in Example 6, (5.8 g) of 4-(4'-fluorobenzoyl)isophthalic acid and 3-(4'-fluorobenzoyl)-terephthalic acid in diethylene glycol dimethyl ether (29 ml) at 20-25°C, and the mixture was stirred for 10 min. Thereto was added dropwise boron trifluoride-THF complex (10.9 g) at 20-45°C,

and the mixture was heated at 40-50°C for 2 hr. After hydrolysis with water (50 ml) in an ice bath, 85% phosphoric acid (50 ml) was added, and the mixture was stirred at 60°C for 5 hr. Water (200 ml) was added and the mixture was cooled. The generated crystals were collected by filtration, washed with water and dried to give crude 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (3.23 g). This was recrystallized twice from toluene to give nearly pure 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (2.10 g, 43%).

melting point 101-104°C

IR(KBr) ν=3214(br), 2848(w), 1606(s), 1511(s), 1225(s), 1157(m), 1135(m), 1046(s), 1015(s), 824(s), 810(s), 783(m) cm^{-1}

^{1}H-NMR($CDCl_3$, 400 MHz) δ=4.72(2H,s), 5.19(1H,d,J=12Hz), 5.31(1H,d,J=12Hz), 6.14(1H,s), 6.98(1H,d,J=8Hz), 7.03(2H,t,J=9Hz), 7.24(1H,d,J=8Hz), 7.29(2H,dd,J=9Hz,J=6Hz), 7.32(1H,s)ppm

Example 9

Synthesis of 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (compound III)

To a suspension of sodium borohydride (14.6 g) dispersed in THF (120 ml) was added dropwise at 20-30°C a solution of a 7:3 mixture (24.0 g), obtained in the same manner as in Example 6, of 4-(4'-fluorobenzoyl)isophthalic acid and 3-(4'-fluorobenzoyl)-terephthalic acid in THF (240 ml). The mixture was heated to 55°C and thereto was added dropwise dimethyl sulfate (47.0 g) at 55-65°C. After the dropwise addition, the mixture was refluxed for 5 hr, and hydrolyzed with water (72 ml) in an ice bath. THF was evaporated under reduced pressure. To the residue was added 85% phosphoric acid (48 g) and the mixture was stirred at 60°C for 5 hr. Water (72 ml) was added and the mixture was cooled. The generated crystals were collected by filtration, washed with water and dried to give crude 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (15.1 g). This was recrystallized twice from toluene to give nearly pure 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (8.2 g, 40%). The various spectrum data of the crystals were the same as those obtained in Example 8.

Example 10

Synthesis of 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (compound III)

To a suspension of sodium borohydride (15.0 g) dispersed in THF (130 ml) was added dropwise at 20-30°C a solution of 4-(4'-fluorobenzoyl)isophthalic acid (26.0 g) synthesized in Example 2 in THF (260 ml) and the mixture was heated to 55°C. Dimethyl sulfate (51.0 g) was added dropwise at 55 - 65°C. After the dropwise addition, the mixture was refluxed for 5 hr, and hydrolyzed with water (130 ml) in an ice bath. THF was evaporated under reduced pressure. To the residue was added 85% phosphoric acid (52 g) and the mixture was stirred at 60°C for 5 hr. Water (390 ml) was added and the mixture was cooled. The generated crystals were collected by filtration, washed with water and dried to give crude 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (20.4 g). This was recrystallized from a mixed solvent of ethyl acetate and heptane (2:3) to give nearly pure 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (18.9 g, 86%). The various spectrum data of the crystals were the same as those obtained in Example 8.

Example 11

Synthesis of 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (compound III)

To a suspension of lithium aluminum hydride (1.0 g) dispersed in THF (10 ml) was added dropwise at room temperature a solution of 4-(4'-fluorobenzoyl)isophthalic acid (3.0 g) in THF (30 ml), and the mixture was stirred for 10 hr. To the reduced reaction mixture was added 10% hydrochloric acid (10 ml) and the mixture was passed through celite. THF was evaporated under reduced pressure, and 85% phosphoric acid (10 g) was added. The mixture was stirred at 60°C for 5 hr. To the reaction mixture was added water (50 ml) and the resulting crystals were collected by filtration and dried. The objective compound was separated by silica gel column chromatography to give 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (0.21 g, 8%). The various spectrum data of the crystals were the same as those obtained in Example 8.

Example 12

Synthesis of 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbaldehyde (compound V)

1-(4'-Fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (299.3 g) and manganese dioxide (2.25 kg, type HMH, manufactured

by Toso) were dispersed in t-butyl methyl ether (3.4 L) and the mixture was stirred at 10-30°C for 6 hr. The reaction mixture was filtered and washed with t-butyl methyl ether (0.9 L). The solvent was evaporated under reduced pressure to give nearly pure 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbaldehyde (258.2 g, 87%) as pale-yellow white crystals.

^{1}H-NMR($CDCl_3$, 400 MHz) δ=5.25(1H,d,J=13Hz), 5.38(1H,d,J=13Hz), 6.18(1H,s), 7.06(2H,t,J=9Hz), 7.16(1H,d,J=8Hz), 7.30(2H,dd,J=9Hz,J=5Hz), 7.77(1H,d,J=8Hz), 7.83(1H,s), 10.03(1H,s)ppm

Example 13

Synthesis of 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile (compound VI)

1-(4'-Fluorophenyl)-1,3-dihydrobenzofuran-5-ylmethanol (50.0 g) and manganese dioxide (200 g, type HMH, manufactured by Toso) were dispersed in xylene (400 ml) and the mixture was stirred at 25-45°C for 6 hr. The reaction mixture was filtered, and hydroxylamine hydrochloride (14.1 g) and triethylamine (20.5 g) were added. The mixture was stirred at 70-75°C for 1 hr and acetic anhydride (75.3 g) was added. The mixture was stirred at 130-140°C for 6 hr and water (180 ml) was added to the reaction mixture. Thereto was added 10% aqueous sodium hydroxide solution (100 g) and the mixture was partitioned. The solvent was evaporated under reduced pressure, and xylene (44 ml) and heptane (71 ml) were added at 60°C. The mixture was cooled to room temperature and the resulting crystals were collected by filtration and dried to give 1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile (35.8 g, 73%) as pale-yellow crystals.

melting point 96-98°C

IR(KBr) ν=3050(w), 2867(m), 2228(s), 1603(s), 1510(s), 1224(s), 1157(m), 1048(s), 1031(s), 832(s)cm^{-1}

^{1}H-NMR($CDCl_3$, 400 MHz) δ=5.21(1H,d,J=13Hz), 5.34(1H,d,J=13Hz), 6.16(1H,s), 7.06(2H,t,J=9Hz), 7.10(1H,d,J=8Hz), 7.27(2H,dd,J=9Hz,J=5Hz), 7.55(1H,d,J=8Hz), 7.60(1H,s)ppm

Comparative Example 1

Synthesis of 4-(4'-fluorobenzoyl)isophthalic acid (compound II)

Trimellitic anhydride (20 g) and fluorobenzene (20 g) were

dispersed in nitrobenzene (200 ml) and anhydrous aluminum chloride (45 g) was added. The mixture was stirred at 70-90°C for 6 hr. The reaction mixture was analyzed by HPLC, and as a result, 4-(4'-fluorobenzoyl)isophthalic acid was found to have been generated by 4%. The mixture was further stirred at 110-120°C for 6 hr, but only the by-product (other than isomer) increased and the production rate of 4-(4'-fluorobenzoyl)isophthalic acid showed a propensity toward decrease.

Reference Example 1

Synthesis of 1-(3'-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram base)

To a suspension of 60% sodium hydride (4.2 g) dispersed in THF (135 ml) was added dropwise at 40-50°C a solution of 1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (21.6 g) in THF (40 ml). The mixture was stirred at the same temperature for 30 min and a solution of 3-dimethylaminopropyl chloride (14.4 g) in t-butyl methyl ether (60 ml) was added dropwise. The mixture was stirred for 10 min and dimethyl sulfoxide (135 ml) was added dropwise. The mixture was stirred at 60-70°C for 5 hr. The reaction mixture was poured into ice water (800 ml) and extracted 3 times with toluene (250 ml). The organic layer was extracted twice with 20% aqueous acetic acid (250 ml). The aqueous layer was neutralized, extracted twice with toluene (250 ml) and washed with water. The solvent was evaporated to give 1-(3'-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram base) as a viscous oil (17.9 g, 61.1%).

^{1}H-NMR($CDCl_3$, 400 MHz) δ=1.26-1.52(2H,m), 2.11-2.26(4H,m), 2.13(6H,s), 5.15(1H,d,J=13Hz), 5.19(1H,d,J=13Hz), 7.00(2H,t,J=9Hz), 7.41(1H,d,J=8Hz), 7.43(2H,dd,J=9Hz,J=5Hz), 7.50(1H,s), 7.59(1H,d,J=8Hz)ppm

This oil was converted to hydrobromide by a conventional method and the obtained crystals had a melting point of 184 - 186°C.

【Effect of the Invention】

According to the present invention, an industrially advantageous production method of 5-phthalancarbonitrile compound affording a high yield can be provided without using a reagent

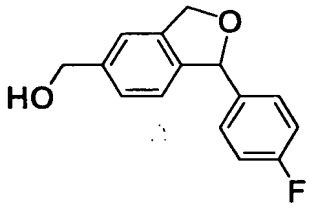
placing a large burden on the environment (small environmental burden), such as heavy metal, metal cyanide and thionyl chloride. Using the 5-phthalancarbonitrile compound obtained in this manner, citalopram useful as an antidepressant can be provided.

【Document】 Abstract

【Abstract】

【Problem】 Provision of a production method of 5-phthalancarbonyl compound, which is safe and causes small environmental burden (without the use of reagent causing great burden on environment such as heavy metal, metal cyanide, thionyl chloride and the like).

【Solving Means】 By a completely new strategy using a compound of the formula III as a key intermediate, a 5-phthalancarbonyl compound is produced.



III

【Main Drawing】 None